



ORIGINAL ARTICLE

Variability of disease activity in patients with hereditary angioedema type 1/2: longitudinal data from the Icatibant Outcome Survey

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Abstract

Background Hereditary angioedema due to C1 inhibitor deficiency (HAE-1/2) is a chronic and debilitating disease. The unpredictable clinical course represents a significant patient burden.

Objective To analyse longitudinal registry data from the Icatibant Outcome Survey (IOS) in order to characterize temporal changes in disease activity in patients with HAE-1/2.

Methods Icatibant Outcome Survey (NCT01034969) is an international observational registry monitoring the clinical outcomes of patients eligible for icatibant treatment. The current analyses are based on data collected between July 2009 and July 2019. Retrospective data for attacks recorded in the 12 months prior to IOS enrolment and for each 12-month period up to 7 years were analysed.

Results Included patients reported angioedema attacks without long-term prophylaxis (LTP; $n = 315$) and with LTP ($n = 292$) use at the time of attack onset. Androgens were the most frequently used LTP option (80.8%). At the population level, regardless of LTP use, most patients (52–80%) reporting <5 attacks in Year 1 continued experiencing this rate; similarly, many patients (25–76%) who reported high attack frequency continued reporting ≥ 10 attacks/year. However, year on year, 31–51% of patients experienced notable changes (increase/decrease of ≥ 5 attacks) in annual attack frequency. Of patients who reported an absolute change of ≥ 10 attacks from Year 1 to 2, 17–50% continued to experience a change of this magnitude in subsequent years.

Conclusion At the population level, attack frequency was generally consistent over 7 years. At the small group level, 28.8–34.5% of patients reported a change in attack frequency of ≥ 5 attacks from Year 1 to Year 2; up to half of these patients continued to experience this magnitude of variation in disease activity in later years, reflecting high intra-patient variability.

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Conflict of interest

M. Maurer is/was recently a speaker and/or advisor for BioCryst, CSL Behring, KalVista, Moxie, Pharming, Pharvaris and Takeda, and has received research funding from BioCryst, CSL Behring, Moxie, Pharming and Takeda. T. Caballero is a member of advisory boards for BioCryst, CSL Behring, Novartis, Octapharma, Pharming and Takeda; is a member of speaker bureaus for CSL Behring, Merck, Novartis and Takeda; has received grants or honoraria from BioCryst, CSL Behring, Novartis and Takeda; has received funding to attend conferences/educational events from CSL Behring, Novartis and Takeda; is/has been a clinical trial/registry investigator for BioCryst, CSL Behring, Novartis, Pharming and Takeda; and is a researcher from the IdiPAZ program for promoting research activities. W. Aberer has acted as a medical advisor/speaker for BioCryst, CSL Behring, Pharming and Takeda; has received research grants from CSL Behring and Takeda; and has received funding to attend conferences/educational events and donations to his departmental fund from and participated in clinical trials for BioCryst and Takeda. A. Zanichelli has received speaker fees from CSL Behring, Sobi and Takeda; consulting fees from CSL Behring and Takeda; and has acted on the medical/advisory boards for CSL Behring and Takeda. L. Bouillet has received honoraria from BioCryst, CSL Behring, Novartis, Pharming and Takeda; and her institute has received research funding from CSL Behring, GlaxoSmithKline, Novartis, Roche and Takeda. A. Bygum has received research grant support and/or speaker/consulting fees from CSL Behring and Takeda and participated in a clinical trial for BioCryst and Takeda; she is an advisor for the HAE Scandinavian Patient Organization. A.S. Grumach has been a speaker/consultant for BioCryst, Biotest, CSL Behring and Takeda. J. Botha and I. Andresen are employees of and hold stock/stock options in Takeda. H.J. Longhurst has received research grant support and/or speaker/consultancy fees from Adverum, BioCryst, CSL Behring, GlaxoSmithKline, Octapharma, Pharming, Pharvaris and Takeda.

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Introduction

Hereditary angioedema with C1 inhibitor deficiency (HAE-1/2) is a rare condition caused by mutations of the *SERPING1* gene. Patients experience unpredictable attacks characterized by vascular oedema in mucosal/submucosal or deep dermal/subcutaneous tissues.^{1,2} Initial symptom onset typically occurs during the first two decades, with patients experiencing recurrent attacks over their lifetime.^{3,4} The unpredictable nature of angioedema attacks places a considerable psychological and socioeconomic burden on the patient.^{5,6} Severity of these attacks can range from mild to severe, with unpredictable disabling effects on activities of daily living^{4,6}; furthermore, laryngeal attacks are life-threatening or fatal if immediate treatment is not obtained.⁷

Therapy options for HAE-1/2 focus on treating the attack as it occurs (acute or on-demand treatment) or by providing either pre-procedural or long-term prophylaxis (LTP) to mitigate the risk of an attack.⁸ Significant developments have been made in the understanding of disease pathophysiology during the last decade.^{9,10} Additionally, advances from treatments exclusively administered in a clinical setting to self-treatment at home became possible through the introduction of innovative therapies and patient education programmes,^{11,12} considerably improving the health-related quality of life of patients with HAE-1/2.^{13,14}

HAE-1/2 is widely held to show considerable variation in disease activity not only between patients but also within patients

over time.^{15–17} Very few recent publications have described the broader clinical picture of how disease activity may manifest and fluctuate (e.g. patients may be free of attacks for years, but then suddenly and without warning may experience a fatal attack). Because of this, the variability of disease is largely unknown. A better understanding of the course of HAE-1/2 over time would be of benefit to patients and healthcare providers alike. Observational drug registries and prospective studies, particularly those involving rare diseases, are an important source of real-world information about the course of a disease.^{18,19} Here, we report longitudinal data from the Icatibant Outcome Survey (IOS), an international registry of patients diagnosed with HAE-1/2 (and other forms of angioedema) who are eligible to receive icatibant to treat their attacks, in order to better characterize the course of HAE-1/2.

Materials and methods

Study design and patients

Icatibant Outcome Survey (ClinicalTrials.gov, NCT01034969) is a prospective observational registry; detailed methodology has been published elsewhere.²⁰ The analyses described herein are based on data collected between July 2009 and July 2019 in patients with HAE-1/2. Retrospective data for attacks recorded in the 12 months prior to IOS enrolment and for each 12-

month period up to 7 years were analysed. A total of 56 centres in 12 countries (Austria, Brazil, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden, and the United Kingdom) contributed to this analysis. Patient demographics and characteristics were recorded at enrolment (IOS entry), including information on HAE attacks before IOS entry, and at routine visits thereafter, recommended to take place approximately every 6 months.

Attack data were captured as previously described.^{20,21} Attack severity was classified as very mild (very mild interference with daily activities), mild (mild interference with daily activities), moderate (moderate interference with daily activities and no other countermeasures required), severe (severe interference with daily activities and with or without other countermeasures), and very severe (very severe interference with daily activities and other countermeasures required). Treated attacks were defined as those receiving acute treatment with icatibant, whereas untreated attacks were defined as those that did not receive any acute treatment. Separate analyses were conducted depending on whether patients were receiving LTP or not at the recorded time of attack onset. No patients were censored, and the same patient may appear in both categories if their use of LTP was initiated, temporarily interrupted or permanently discontinued during follow-up, and if they experienced attacks at different times both without and with LTP.

Icatibant Outcome Survey is conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Approval was obtained from ethics committees and/or local health authorities at all centres.

Statistical analyses

Longitudinal analyses of attack frequency and severity and year-on-year change in disease activity were performed at the population level for each 12-month period from enrolment to 7 years after IOS entry. Small group-level data analyses were conducted to resemble individual patient-level data analyses. Firstly, patients were grouped into three categories based on their attack frequency in Year 1 of IOS follow-up: <5 attacks per year ('low frequency'); 5 to <10 attacks per year ('moderate frequency'); and ≥ 10 attacks per year ('high frequency'). Secondly, the same three categories were used to define absolute change (increase or decrease) in attack frequency compared with the previous year of follow-up (e.g. change from Year 1 to Year 2); an absolute change of <5 attacks from year to year was considered to be a sign of relatively consistent disease activity ('no notable change'), and changes of 5 to <10 attacks and ≥ 10 attacks from year to year were considered to be 'moderate' and 'substantial' changes, respectively, in disease activity. Data are presented as median (range) or mean (SD) and proportions of patients per annual attack frequency/absolute change category.

Results

At the population level, the number and severity of attacks per year do not change substantially over time

The analysis population comprised 315 patients who reported attacks without LTP and 292 patients who reported attacks with LTP during follow-up (Table 1). The majority of patients were diagnosed with HAE Type I and were female. The median (Q1, Q3) delay in diagnosis was 6.4 (0.3, 18.1) years in patients with no prior LTP and 6.6 (0.5, 17.5) years in those with prior LTP. The most frequently received prior LTP was attenuated androgens (80.8%), followed by tranexamic acid (40.1%) and plasma-derived C1-INH (26.4%).

The median number of all attacks, untreated attacks and icatibant-treated attacks per patient per year did not change significantly ($P \geq 0.05$), irrespective of the LTP used (Fig. 1). There were no substantial differences in attack frequency between male and female patients (Table S1, Supporting Information). Mean (standard deviation) number of attacks (overall, untreated and icatibant-treated) were reported in Table S2 (Supporting Information). Categorizing patients into three attack frequency groups (<5, 5 to <10 and ≥ 10 attacks per year) confirmed that disease activity was generally consistent at the population level (Fig. S1, Supporting Information). Attack severity (prior to icatibant treatment) was generally similar over time, with and without LTP; however, slightly higher proportions of patients with LTP had very severe attacks during most years (Fig. 2).

At the small group level, annual attack frequency, grouped by Year 1 rate, suggests that most patients who report either low (<5) or high (≥ 10) annual attack rate continue to experience these frequencies

Most patients (52–80%) with <5 attacks in Year 1 continued to experience low attack frequency in subsequent years (Fig. 3); similarly, 25–76% of patients with ≥ 10 attacks in Year 1 continued to experience high annual attack frequency. For patients who reported 5 to <10 attacks in Year 1, annual attack frequency during subsequent years was variable. There was a general trend towards lower annual attack frequency in patients with LTP compared with those without LTP in the low- and moderate-frequency groups, but not in the high-frequency group.

Absolute change in attack frequency from year to year indicates that up to half of the patients without LTP and up to one-third of patients with LTP experience fluctuating disease activity

Fluctuations in annual attack frequency were evaluated, with change categorized as a difference of <5, 5 to <10 or ≥ 10 attacks from the previous year (Fig. 4).

In patients without LTP, 35% experienced moderate (five to <10) or substantial (≥ 10) changes in the number of attacks from

Table 1 Patient demographics and disease characteristics at IOS entry by LTP use at the time of HAE attacks during IOS follow-up

Characteristic	Patients who had attacks without LTP (n = 315)	Patients who had attacks with LTP (n = 292)
HAE diagnosis, n (%)		
Type 1	292 (92.7)	280 (95.9)
Type 2	23 (7.3)	12 (4.1)
Sex, n (%)		
Female	201 (63.8)	164 (56.2)
Male	114 (36.2)	128 (43.8)
Age at enrolment, years		
n (missing)	315 (0)	292 (0)
Median (Q1, Q3)	38.4 (26.0, 51.0)	39.5 (28.3, 50.8)
Min, max	16.4, 81.3	15.3, 80.3
Age at onset of symptoms, years		
n (missing)	277 (38)	241 (51)
Median (Q1, Q3)	13.0 (6.0, 19.0)	10.0 (5.0, 18.0)
Min, max	0.2, 72.0	0.2, 67.0
Age at diagnosis, years		
n (missing)	303 (12)	266 (26)
Median (Q1, Q3)	21.1 (13.1, 34.6)	20.7 (13.6, 32.3)
Min, max	0.0, 74.2	0.0, 69.2
Delay between onset of symptoms and diagnosis, years		
n (missing)	275 (40)	234 (58)
Median (Q1, Q3)	6.4 (0.3, 18.1)	6.6 (0.5, 17.5)
Min†, max	−19.0, 61.0	−41.8, 66.9
Countries with ≥10% of enrolled patients in either LTP subgroup, n (%)		
France	64 (20.3)	97 (33.2)
Germany	56 (17.8)	11 (3.8)
Spain	49 (15.6)	62 (21.2)
UK	37 (11.7)	54 (18.5)
Type of LTP received‡, n (%)		
Attenuated androgens†		236 (80.8)
Tranexamic acid		117 (40.1)
Plasma-derived C1-INH†		77 (26.4)
Recombinant C1-INH		6 (2.1)
C1-INH (unspecified form)		2 (0.7)
Other		50 (17.1)

C1-INH, C1 inhibitor; HAE, hereditary angioedema; IOS, icatibant outcome survey; LTP, long-term prophylaxis; max, maximum; min, minimum; Q, quartile.

† Negative delay determined in patients diagnosed before symptoms due to family history. ‡Patients can be listed in more than one category if they use different types of LTP during separate HAE attacks. §Danazol (n = 178, 61.0%), stanozolol (n = 50, 17.1%) or oxandrolone (n = 8, 2.7%). ¶Intravenously administered.

Year 1 to Year 2; in the subsequent years, this proportion varied between 31% and 51%. In patients with LTP, the proportion reporting no notable change was slightly higher and more consistent than in patients without LTP, whereas the proportion

reporting a substantial change was generally lower at each time point.

Absolute change in attack frequency, grouped by difference from Year 1 to Year 2, suggests that patients with a notable change after the first year continue to experience fluctuating disease activity

Between 43% and 80% of patients without a notable change in attack frequency from Year 1 to Year 2 continued to report little change in subsequent years; 43–70% of patients without LTP and 52–80% of patients with LTP continued to report no notable change (Fig. 5). Patients with a change of five to <10 attacks from Year 1 to Year 2 experienced variable changes in attack frequency in subsequent years, particularly those without LTP; the number of patients per year in this category was small ($n \leq 17$). The absolute change in attack frequency was particularly inconsistent for patients without LTP, for whom changes of five or more attacks from year to year ranged from 50% to 77% up to Year 5. Between 17% and 50% of patients with an absolute change of ≥ 10 attacks from Year 1 to 2 continued to experience a substantial change up to Year 6; again, the number of patients per year in this category was small ($n \leq 14$).

Discussion

This is the first report of longitudinal IOS data, without reference to icatibant treatment outcomes, to characterize the variability of disease in a large international cohort of patients with HAE-1/2. The initial onset of clinical symptoms in this cohort, during early to late adolescence, is consistent with previous non-IOS studies in patients with HAE-1/2.^{15,17,22,23} The high variability in attack frequency observed in many IOS patients is generalizable to the wider population of patients with HAE-1/2,⁴ and reflects the need for patients and physicians to continually evaluate disease activity and ensure that acute treatment can be accessed and LTP, when needed, is optimized.

At the population level, the frequency and severity of attacks per patient per year following IOS enrolment were generally consistent over the 7-year analysis period, confirming the chronic nature of the disease. Categorizing patients by their attack frequency in Year 1 and absolute change into Year 2 allowed small group-level analyses that could infer outcomes comparable with individual patient-level data analyses. An absolute change (increase or decrease) of five or more attacks during Year 1 was experienced by approximately one-third of the patients. Use of LTP did not mitigate this fluctuation in disease activity in a consistent manner over time. Of these patients, between one-third and one-half continued to experience moderate or substantial changes in annual attack frequency for the next 5 years. In contrast, most patients with an absolute change of <5 attacks in Year 1 showed little change in attack frequency during the subsequent 3 years; however, greater proportions of patients reported changes of five or more attacks in the last 2 years of

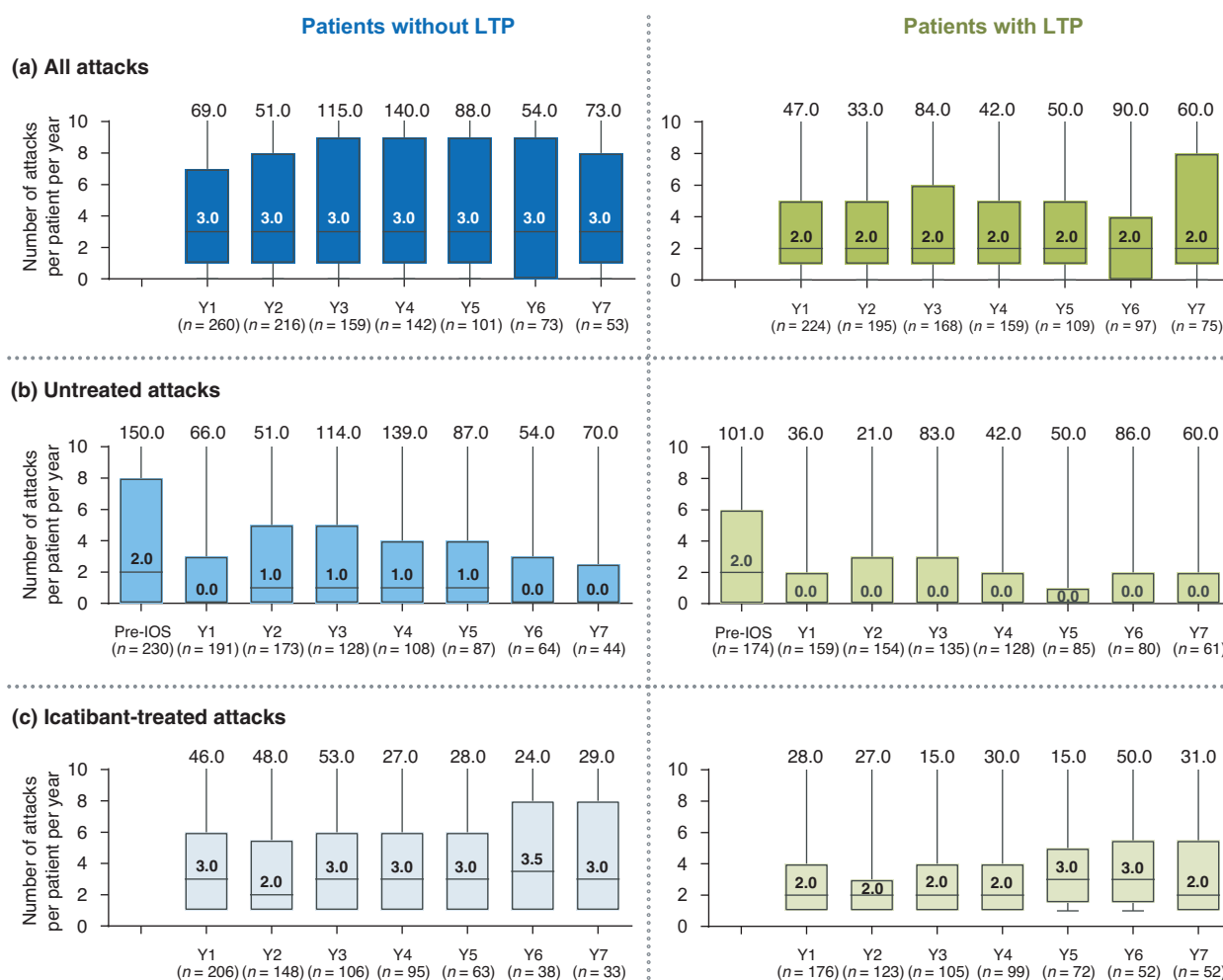


Figure 1 Median (range) number of (a) overall attacks, (b) untreated attacks and (c) icatibant-treated attacks per patient per year of follow-up. The minimum number of attacks per patient per year at all time points was zero for treated and untreated attacks and one for icatibant-treated attacks. *n* indicates the number of patients at each time point. Y1 begins at IOS entry and refers to the first year of follow-up; pre-IOS refers to 12 months before IOS entry. Comparing the median number of attacks per year from Y2 to Y7 with Y1 (Wilcoxon signed-rank test), $P \geq 0.05$ for all years and all subgroup categories. IOS, Icatibant Outcome Survey; LTP, long-term prophylaxis; Y, Year.

follow-up. These results suggest that although disease activity may be more or less consistent for many patients, those who report a notable change in annual attack frequency may continue to experience changes of similar magnitude for several years. Interestingly, we noted a higher number of untreated attacks in the year prior to IOS entry (presumably when few patients had access to icatibant and, thereby, self-administration was more difficult) than in subsequent years.

Disease activity was generally as expected in patients experiencing attacks without and with LTP, with smaller proportions of the 'with LTP' group reporting high annual frequency (≥ 10

attacks per year) or a substantial absolute change (≥ 10 attacks) year on year, although there were trends towards greater proportions of patients with LTP reporting very severe attacks. The latter finding is somewhat surprising (given that one of the aims of LTP is to reduce attack severity),²⁴ potentially highlighting unmet needs with LTP agents available at the time of the survey. Importantly, guidelines recommend that LTP is considered in all severely symptomatic patients,² and the subgroup of patients reporting attacks with LTP may represent those with more severe underlying disease in the absence of any preventative treatment. Interestingly, patients without LTP who fell within the

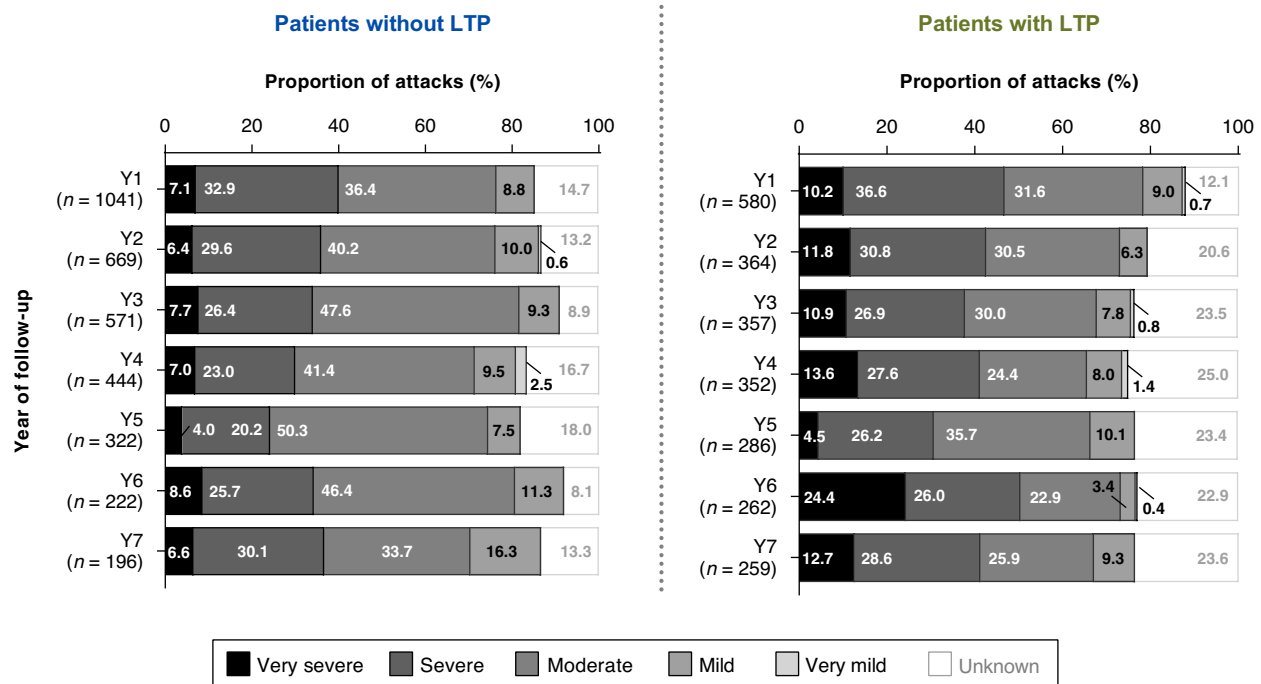


Figure 2 Population-level attack severity (icatibant-treated attacks only; severity recorded prior to treatment) per year. *n* indicates the number of icatibant-treated attacks at each time point. Y1 begins at Icatibant Outcome Survey entry and refers to the first year of follow-up. LTP, long-term prophylaxis; Y, Year.

intermediate categories of moderate attack frequency (5 to <10 attacks in Year 1) or moderate absolute change (5 to <10 attacks from Year 1 to 2) were more likely to report subsequent higher attack frequency or higher absolute change, respectively, compared with patients with LTP in the same categories. In line with these findings, results from a study published in 2011 evaluating Italian patients with HAE showed that patients receiving LTP with androgens continued to experience attacks during the treatment period, although the frequency of attacks was reduced compared with previous periods without LTP.²⁵

The unpredictable nature of HAE-1/2 is well known. In a foundational review of the clinical course of 30 patients with HAE, Frank *et al.*²⁶ describe a great variability of attack frequency where patients may have no attacks for long periods of time, followed by many in rapid succession, as well as patients who may have attacks every few weeks. A retrospective study of 209 German patients published in 2006 by Bork *et al.*¹⁵ reported that although 158 (75.6%) did not have attack-free intervals of >12 months, the remaining 51 patients had symptom-free periods for an average of 7.4 years; 36 of these patients were not receiving prophylaxis and thus the attack-free periods were considered part of their natural disease course. Inter-patient variability in attack frequency was also noted by Bygum,²⁷ Agostoni, and Cicardi, Winnewisser *et al.* and Jolles *et al.*^{16,22,28} Although

this unpredictability from patient to patient has been widely reported, the current findings provide new insights into intra-patient variability. Although a number of life events and concomitant treatments have been identified as triggers for HAE attacks,² most attacks have no known trigger.²⁹ Exposure to unidentified triggers is likely to vary over time and may contribute to the heterogeneity of disease activity. Consistent with updated guideline recommendations for the management of HAE, these data reflect the unpredictable course of the disease over an individual patient's lifetime and highlight the importance of (i) continual reassessment of disease activity and LTP at each visit, (ii) patients carrying on-demand medication at all times (including those receiving LTP), (iii) individualized action plans and treatment plans and (iv) patient awareness of possible attack triggers.^{2,24}

The findings of this study should be interpreted in the context of available LTP options during the follow-up period and treatment patterns in the participating countries. A greater proportion of patients in Germany reported having attacks without LTP than with LTP, consistent with previous findings from IOS that noted differing LTP treatment patterns in Germany compared with patients from other IOS countries.³⁰ The most commonly used LTP therapies in this study were attenuated androgens and tranexamic acid, despite known risks with the

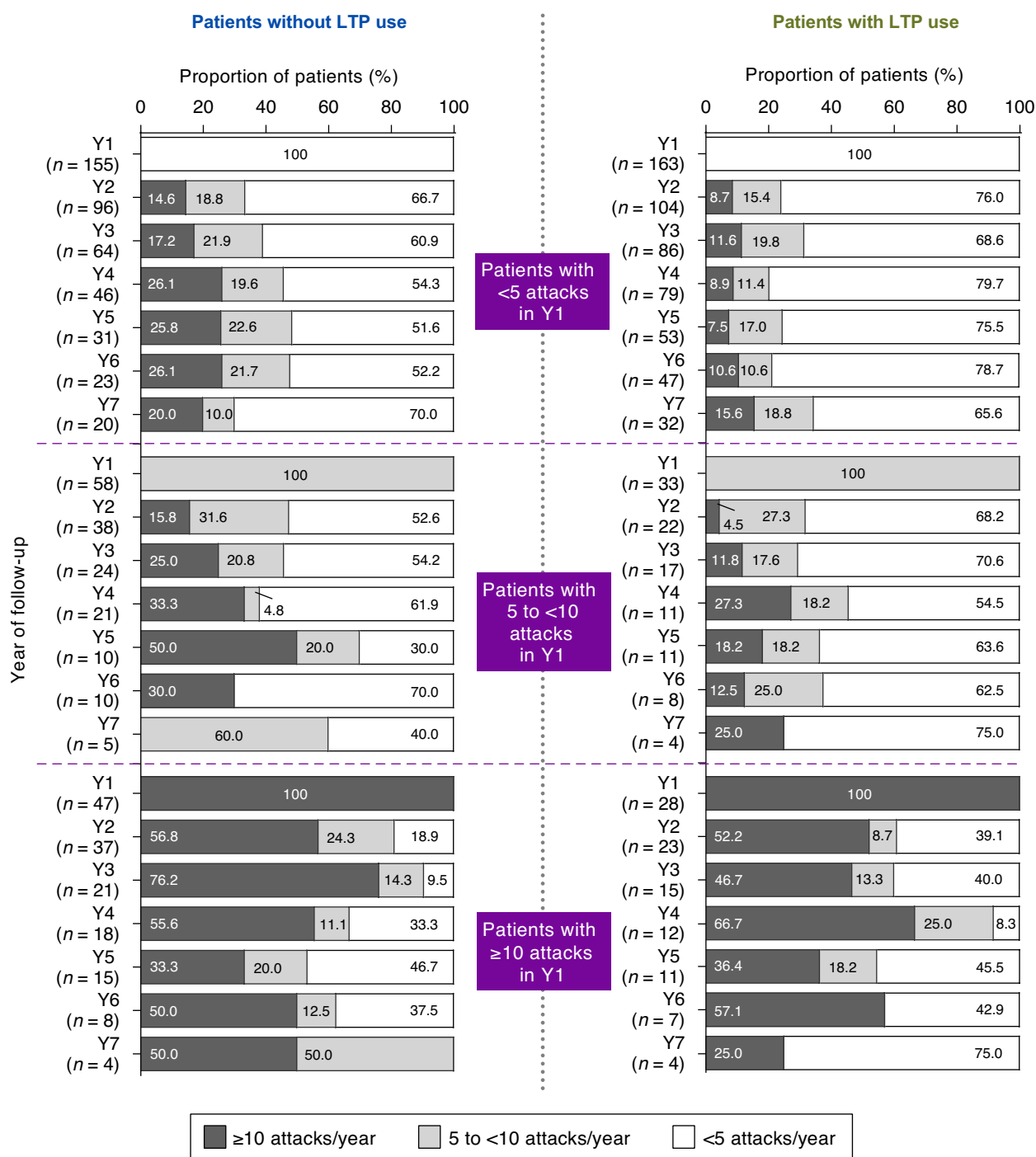


Figure 3 Proportions of patients in three attack frequency categories (<5, 5 to <10 and ≥10 attacks per year) grouped by the number of attacks in Y1. *n* indicates the number of patients at each time point. Y1 begins at Icatibant Outcome Survey entry and refers to the first year of follow-up. LTP, long-term prophylaxis; Y, Year.

former and a lack of recommendation for the latter.³¹ Only a quarter of patients were receiving intravenous plasma-derived C1 inhibitor at the time of reported attack. Recent advances in

the availability of LTP options with improved efficacy, safety and/or convenience, such as plasma kallikrein inhibitor lanadelumab and a subcutaneous formulation of C1 inhibitor,²⁴ were

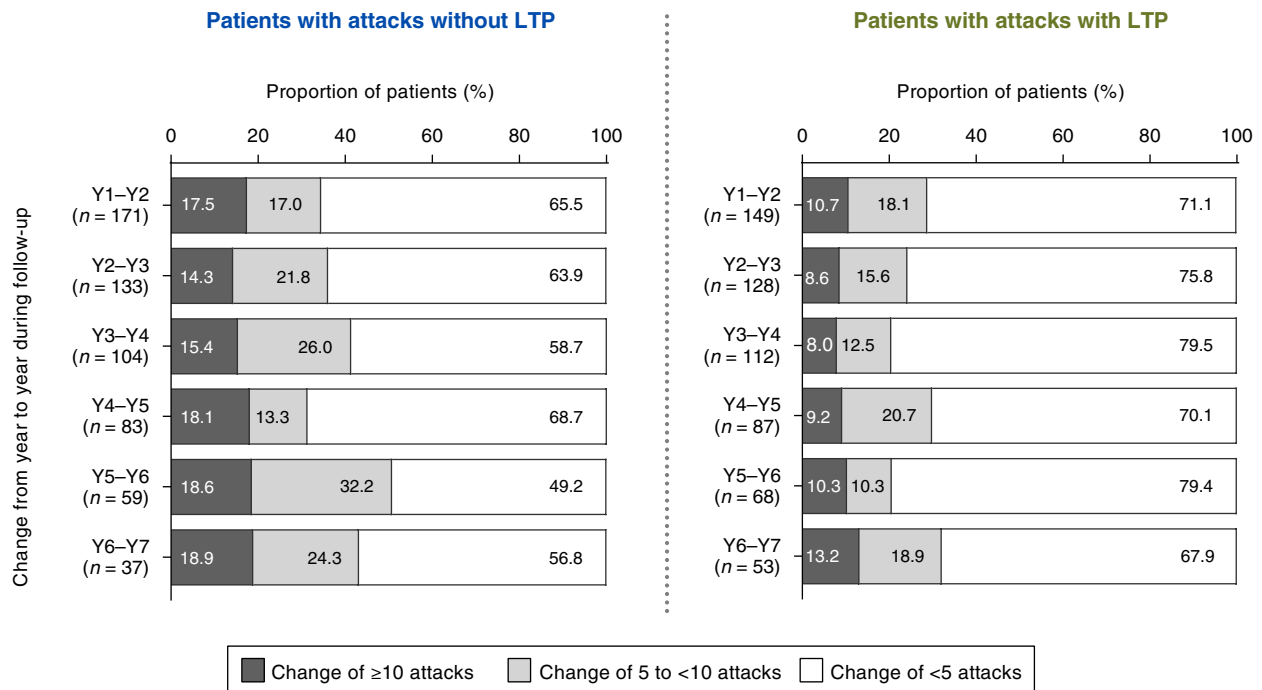


Figure 4 Absolute change in attack frequency from year to year by category (<5, 5 to <10 and ≥10 attacks). *n* indicates the number of patients at each time point; the same patient may be included in both the ‘without LTP’ and ‘with LTP’ groups for different attacks. Y1 begins at Icatibant Outcome Survey entry and refers to the first year of follow-up; Y1–Y2 refers to the absolute change in the number of attacks from Y1 to Y2. LTP, long-term prophylaxis; Y, Year.

not accounted for in this analysis. These newly available therapies may have a greater impact on attack severity and frequency than the LTP treatments most frequently used in this study.

The limitations of these analyses include the use of group-level analyses to closely resemble outcomes of individual patient-level analyses, which were not feasible using IOS data. Insights into disease activity in paediatric patients would be of interest because of increased attack rates observed during puberty;³ however, only nine patients <18 years of age contributed data, and a robust subgroup analysis was not possible. The high number of attacks recorded in the 12 months prior to IOS enrolment compared with attacks while enrolled in IOS was driven by a large number of untreated attacks for which an attack start date is not known. Unlike icatibant-treated attacks, untreated attacks are assumed to have occurred in that 12-month period; thus, this is a limitation of this method of collecting retrospective data. Nevertheless, attacks occurring during IOS enrolment, for which attack start dates were generally available, clearly show that over the 7-year period, the median number of attacks per patient per year was generally consistent. However, individual patients may experience unpredictable changes in attack frequency and/or severity over time, including the occurrence of life-threatening attacks. Use of LTP was only considered at the recorded time of

attack onset; some types of LTP may have a preventative effect for a longer window of time, which was not accounted for in this analysis. Further limitations are typical of registry-based studies using data derived from patient recall, which may be open to patient interpretation.

Conclusions

This study of longitudinal data from IOS aimed to characterize the variability of disease activity in patients with HAE-1/2. Although notable changes in attack frequency in the large overall population were not observed, a deeper analysis at the small group level provided novel insights into how the clinical course of HAE-1/2 may fluctuate unpredictably for select patients. Although attack frequency was consistent for some throughout the 7-year follow-up period, up to one-half of patients without LTP and up to one-third of patients with LTP experienced considerable changes during the first year of IOS enrolment, with many patients in these subgroups continuing to experience fluctuating disease activity during subsequent years. These findings highlight the importance of patients being provided with and carrying acute treatment at all times and may help inform patient and physician decisions regarding the management of this unpredictable and chronic disease.

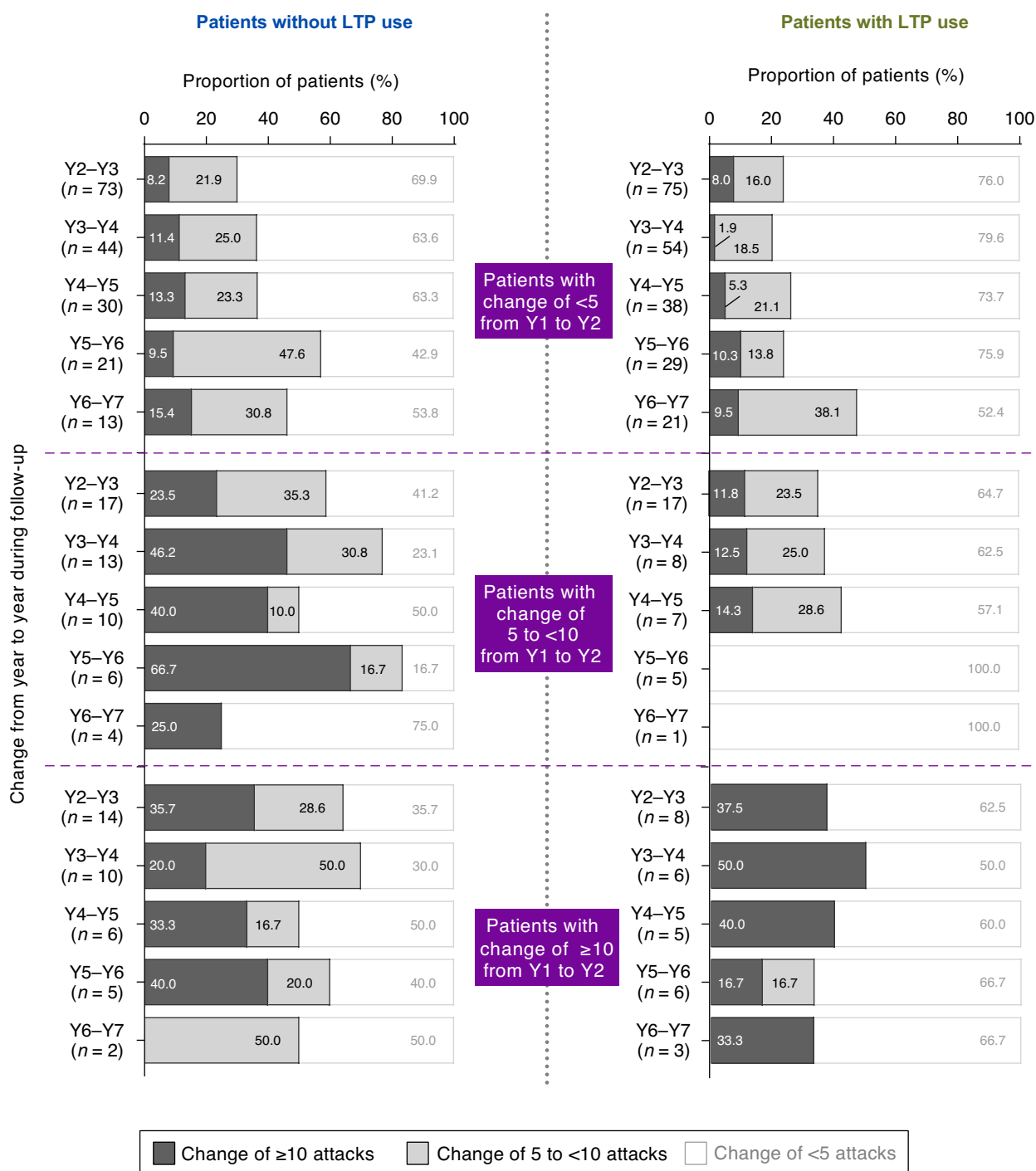


Figure 5 Proportions of patients with absolute change in attacks from year to year, grouped by change in attack frequency during Y1–Y2. *n* indicates the number of patients at each time point; the same patient may be included in both the ‘without LTP’ and ‘with LTP’ groups for different attacks. Y1 begins at Icatibant Outcome Survey entry and refers to the first year of follow-up; Y1–Y2 refers to the absolute change in the number of attacks from Y1 to Y2. Numbers may not add up to 100% due to rounding. LTP, long-term prophylaxis; Y, Year.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Population-level attack frequency per year by category (less than five, five to <10 and ≥10 attacks per year). *n* indicates the number of patients at each time point.

Table S1. Median (IQR) number of overall attacks, untreated attacks and icatibant-treated attacks per patient per year of follow-up.

Table S2. Mean (SD) number of overall, untreated and icatibant-treated attacks per patient per year of follow-up.